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Highly Ortho-Selective Cross-Coupling of Dichlorobenzene Derivatives with Grignard Reagents

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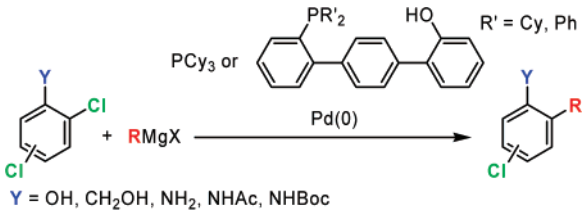
ABSTRACT



Highly ortho-selective cross-coupling of dichlorobenzene derivatives with Grignard reagents was realized using a combination of $Pd_2(dba)_3$ and PCy_3. Use of hydroxylated terphenylphosphines further improved the reactions of dichlorophenol and dichloroaniline.

Cross-coupling of haloarenes with organometallic reagents constitutes one of the most important and practical reactions among transition-metal-catalyzed C−C bond formations.[1] However, when arene molecules have more than one substituent of the same halogen atom, transition-metal-catalyzed site-selective cross-coupling involving site-selective conversion of one of the halogen atoms to another group remains relatively unexplored. For dihalogenated heteroarenes, many examples of site-selective cross-coupling exist.[2] In contrast, only a few examples have been reported for dihalogenated benzene derivatives.[3] Although the reactions reported can be useful, developing other strategies for site selection is of great interest.

Recently, we reported ortho-selective cross-coupling of dibromophenols or dibromoanilines with Grignard reagents in the presence of Pd catalysts.[4] Reaction selectivity is controlled by catalysts generated from hydroxylated terphenylphosphine ligands such as **1** and **2**.[5,6] Other phosphines did not promote the ortho-selective reactions. It is worth noting that these reactions occurred at positions ortho to highly electron-donating groups such as -OMgBr and -NHMgBr. This ortho-selectivity was not expected from the previous examples of site-selective cross-coupling.[7,8] To expand the scope of coupling, we next investigated reactions of di*chloro*benzene derivatives and found that the dichloro derivatives showed behavior different from dibromo deriva-

(1) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.

(2) A review: Schröter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245.

(3) (a) Singh, R.; Just, G. *J. Org. Chem.* **1989**, *54*, 4453. (b) Ishii, Y.; Chatani, N.; Yorimitsu, S.; Murai, S. *Chem. Lett.* **1998**, *27*, 157. (c) Dirk, S. M.; Price, D. W., Jr.; Chanteau, S.; Kosynkin, D. V.; Tour, J. M. *Tetrahedron* **2001**, *57*, 5109. (d) Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964. (e) Ackermann, L.; Althammer, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1627. (f) Houpis, I. N.; Hoeck, J.-P. V.; Tilstam, U. *Synlett* **2007**, 2179. MeO as a leaving group: (g) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706. For an example of selective cross-coupling of 1,2-dihaloalkenes, see: (h) Bellina, F.; Anselmi, C.; Viel, S.; Mannina, L.; Rossi, R. *Tetrahedron* **2001**, *57*, 9997. For early examples of selective cross-coupling of 1,1-dihaloalkenes, see: (i) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (j) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541. For enantioposition-selective cross-coupling, see: (k) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101. Cu-catalyzed intramolecular etherification of bisvinylbromides: (l) Fang, Y.; Li, C. *J. Am. Chem. Soc.* **2007**, *129*, 8092.

(4) Ishikawa, S.; Manabe, K. *Chem. Lett.* **2007**, *36*, 1304.

(5) (a) Ishikawa, S.; Manabe, K. *Chem. Lett.* **2007**, *36*, 1302. Ligand **1** was purified as its HBF_4 salt, and the salt was used directly in coupling reactions in which the free phosphine was liberated. For an HBF_4 salt, see: (b) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(6) Ligands **1** and **2** were designed on the basis of biphenylphosphines such as **11** developed by Buchwald et al. See: Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.

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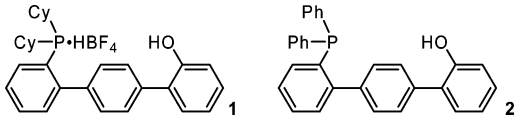
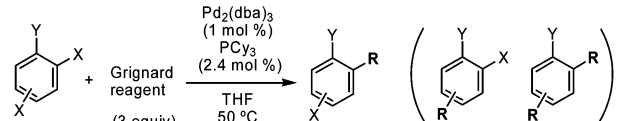
tives. Here, we reveal a new type of site-selective cross coupling in which complete ortho-selectivity was realized even with a simple phosphine, tricyclohexylphosphine (PCy_3). Moreover, use of **1** or **2** further improved reactions of dichlorophenol and dichloroaniline.

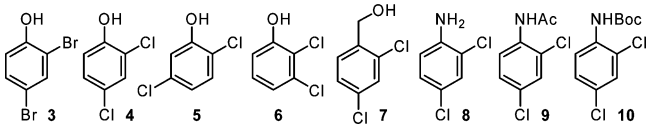


The reaction of 2,4-dichlorophenol (**4**) with 4-methoxyphenyl Grignard reagent was examined first.[9] Remarkably, the catalyst generated from $Pd_2(dba)_3$ and PCy_3 afforded the ortho-arylated compound in good yield (Table 1, entries 2 and 3). Neither the isomeric monoarylated compound (**isomer**) nor the diarylated compound (**di**) was obtained. This result is contrary to the reaction of dibromophenol, which produced significant amounts of **isomer** and **di** (entry 1).[4] Formation of diarylated compounds often are unavoidable in cross-coupling reactions,[10] and even in our previous ortho-selective reactions of dibromobenzene derivatives using **1**,[4] complete suppression of diarylation could not be achieved. Thus, the absence of **di** is worth noting. The complete ortho-selectivity was also observed for compound **5** (entry 6). The result is worth mentioning because cross-coupling occurred at more electronically negative and more sterically hindered carbons. Compound **6** was not reactive under these conditions, probably because of the steric hindrance of *o*-Cl (entry 7). Not only the OH group but also other directing groups such as CH_2OH, NH_2, NHAc, and NHBoc worked well to produce ortho-arylated products (entries 8−11).[11]

Table 1. Ortho-Selective Cross-Coupling of Dihalobenzene Derivatives

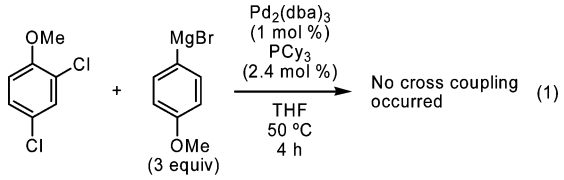


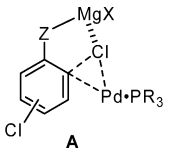
entry	dihalobenzene derivatives	Grignard reagent	reaction time (h)	yield (%) ortho	isomer	di
1[a]	**3**	4-$MeOC_6H_4MgBr$	24	21	14	38
2	**4**	4-$MeOC_6H_4MgBr$	4	80	0	0
3	**4**	4-$MeOC_6H_4MgBr$	18	91	0	0
4	**4**	PhMgCl	4	85	0	0
5	**4**	2-ThienylMgBr[b]	20	52	0	0
6[c]	**5**	4-$MeOC_6H_4MgBr$	18	95	0	0
7	**6**	4-$MeOC_6H_4MgBr$	4	1	0	0
8	**7**	4-$MeOC_6H_4MgBr$	18	99	0	0
9[c]	**8**	4-$MeOC_6H_4MgBr$	18	87	0	0
10	**9**	4-$MeOC_6H_4MgBr$	4	71	0	0
11[c]	**10**	4-$MeOC_6H_4MgBr$	8	55	0	0



[a] At 25 °C with 4 equiv of the Grignard reagent. [b] 4 equiv. [c] $Pd_2(dba)_3$ (2 mol %) and PCy_3 (4.8 mol %) were used.

The reaction of 2,4-dichloroanisole under the same conditions did not give the cross-coupled products as shown in eq 1. This result strongly suggests that the presence of a protic group in the substrates is essential for rate acceleration at the ortho-position. The requirement of a protic group seems counterintuitive, because the presence of an anionic substituent formed by deprotonation with a Grignard reagent should retard oxidative addition due to the strong electron-donating ability.[12] To explain the acceleration at the ortho-position, we propose transition state **A**, in which Lewis acidic Mg facilitates oxidative addition of the *o*-C−Cl bond to Pd.[13] On the other hand, we cannot exclude the possibility that





(7) In most of the reported examples, the reactions were mainly controlled by the electronic property of the substrates: the reactions occur preferentially at less electronically negative carbons. For example, selective Sonogashira coupling of dibromoanilines, which has an electron-donating NH_2 group, occurred preferentially at the meta-position over the ortho- or para-position.[3a] See also: Fahey, D. R. *J. Am. Chem. Soc.* **1970**, *92*, 402.

(8) Electron-withdrawn groups such as nitro and carboxylato groups are known to facilitate cros- coupling at the ortho-position. This effect has been attributed to coordination of these groups to Pd in the oxidative addition of the *o*-C−X bond: (a) Kim, Y. M.; Yu, S. *J. Am. Chem. Soc.* **2003**, *125*, 1696. (b) Bahmanyar, S.; Borer, B. C.; Kim, Y. M.; Kurtz, D. M.; Yu, S. *Org. Lett.* **2005**, *75*, 1011. (c) Widdowson, D. A.; Wilhelm, R. *Chem. Commun.* **2003**, 578. See also ref 3b.

(9) Reviews on cross-coupling with Grignard reagents: (a) Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: West Sussex, 2004; p 335. (b) Cepanec, I. *Synthesis of Biaryls*; Elesevier: Oxford, 2004, p 83.

(10) (a) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.-i.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958. See also: (b) Sinclair, D. J.; Sherburn, M. S. *J. Org. Chem.* **2005**, *70*, 3730. (c) Dong, C.-G.; Hu, Q.-S. *J. Am. Chem. Soc.* **2005**, *127*, 10006.

(11) Ortho-selective Suzuki−Miyaura coupling of these substrates was not successful. For example, a reaction of **4** with 4-$MeOC_6H_4B(OH)_2$ in the presence of $Pd_2(dba)_3$ (2 mol%), PCy_3 (4.8 mol%), and KF (3 equiv) in THF at 70 °C for 21 h gave **ortho** (32%), **isomer** (14%), and **di** (12%). For Suzuki−Miyaura coupling using these conditions, see: Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

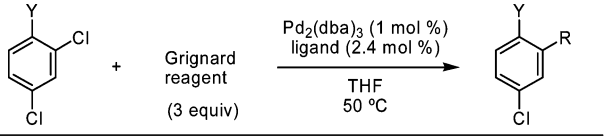
(12) Examples of cross-coupling of halophenols with Grignard reagents: (a) Jendralla, H.; Chen, L.-J. *Synthesis* **1990**, 827. (b) Bumagin, N. A.; Luzikova, E. V. *J. Organomet. Chem.* **1997**, *532*, 271. (c) Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889. An example of Suzuki−Miyaura coupling of 2-halophenols: (d) Wawrzyniak, P.; Heinicke, J. *Tetrahedron Lett.* **2006**, *47*, 8921.

(13) Activation of C−X bonds by coordination to Mg was reported by Nakamura et al. in their Ni-catalyzed cross coupling of ArF or ArCl with Grignard reagents: Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 17978.

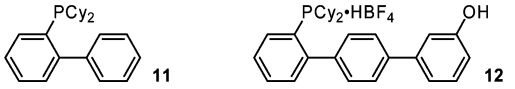
coordination of the anionic directing groups toward Pd stabilizes transition states of ortho-oxidative addition,[8] especially for **7**, **9**, and **10**, which might form five- or six-membered rings by coordination of the anionic oxygen atom to Pd.

To further improve the catalytic system, we used ligands **1** and **2** instead of PCy_3 (Table 2).[14] As expected, **1** and **2** accelerated ortho-selective reaction compared with PCy_3 (entries 1−3 vs Table 1, entry 2). Similar ligands such as **11**[6] and **12**[5a] did not exhibit high activity (entries 4 and 5), indicating that the presence and the position of the OH group of **1** were important for the high activity. Use of **1** was also beneficial for reaction of dichloroaniline **8** (entry 6 vs Table 1, entry 9). Other aryl and alkenyl Grignard reagents also worked well (entries 7−9). Neither para-arylated isomers nor the diarylated compounds were obtained in any of the reactions. Note that a Grignard reagent with a chloro substituent afforded the desired product in an acceptable yield (entry 8), while small amounts of oligomeric byproducts were formed. Alkyl Grignard reagents such as BuMgCl did not afford the desired product (entry 10); instead, a large amount of 4-chlorophenol was produced. For substrates **7**, **9**, and **10**, the acceleration effect of **1** was not observed (data not shown), with PCy_3 better than **1**.

Table 2. Ortho-Selective Cross-Coupling Using **1**, **2**, and Reference Ligands



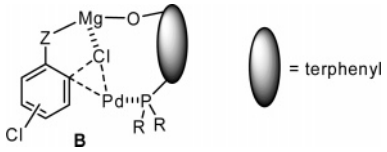
entry	Y	Grignard reagent	ligand	reaction time (h)	yield (%)
1	OH (**4**)	4-$MeOC_6H_4MgBr$	**1**	2	88
2	OH (**4**)	4-$MeOC_6H_4MgBr$	**1**	4	99
3	OH (**4**)	4-$MeOC_6H_4MgBr$	**2**	2	84
4	OH (**4**)	4-$MeOC_6H_4MgBr$	**11**	4	16
5	OH (**4**)	4-$MeOC_6H_4MgBr$	**12**	4	16
6	NH_2 (**8**)	4-$MeOC_6H_4MgBr$	**1**	4	93
7	OH (**4**)	2-ThienylMgBr[a]	**1**	20	73
8	OH (**4**)	4-ClC_6H_4MgBr[b]	**1**	13	63
9[c]	OH (**4**)	Me_2C=CHMgBr	**1**	24	66
10	OH (**4**)	BuMgCl	**1**	24	0



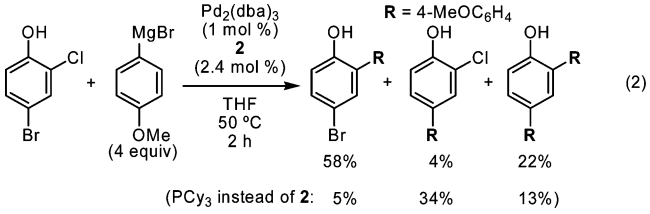
[a] 4 equiv. [b] A solution in Et_2O was used. [c] $Pd_2(dba)_3$ (2 mol %) and **1** (4.8 mol %) were used.

(14) Nakamura et al. also used a phosphine with a hydroxy group for Ni-catalyzed cross-coupling. See ref. 13.

Although the mechanism of acceleration by **1** and **2** is unclear, we speculate formation of transition state **B**, in which coordination of the oxido group of **1** or **2** to the Mg cation places the Pd atom close to the *o*-C−Cl bond. Since **7**, **9**, and **10** were poor substrates and **12** was a poor ligand, subtle changes in the position of Mg and the oxido group may be detrimental to the proper arrangement of the reacting species.



Finally, we demonstrated effectiveness of the hydroxylated phosphines for reaction of 4-bromo-2-chlorophenol (eq 2). Surprisingly, the Cl group at the ortho-position reacted preferentially over the Br group. This unusual selectivity was not observed in the reaction with PCy_3.



In summary, we have developed a method for achieving ortho-selective cross-coupling of dichlorobenzene derivatives with Grignard reagents. Combining use of Pd(0) and PCy_3 realized high selectivity for substrates with directing groups such as OH, CH_2OH, NH_2, NHAc, and NHBoc. Furthermore, ligands **1** and **2** were more effective than PCy_3 for dichlorophenol and dichloroaniline. Although the mechanism of selectivity remains unknown, the reactions described here provide new routes to synthesize multisubstituted benzene derivatives.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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